APPENDIX A

INDUCING AGENT: ANTIBIOTICS (D1-D3)

D1: Nephron. 1996;74(4):694-700.

Effects of intraperitoneal antibiotics on human peritoneal mesothelial cell growth.

Yen CJ, Tsai TJ, Chen HS, Fang CC, Yang CC, Lee PH, Lin RH, Tsai KS, Hung KY, Yen TS.

Department of Internal Medicine, National Taiwan University, Taipei, ROC.

ABSTRACT: Peritonitis is one of the most frequent complications of continuous ambulatory peritoneal dialysis (CAPD). Necrosis and exfoliation of the mesothelial cell layer of the peritoneum develop during the acute phase of peritonitis. Agents that hamper regeneration of mesothelial cells will cause delayed recovery of the peritoneal surface, which results in continuous exposure of underlying stem cells to the stimulation of growth factors and possibly leads to **peritoneal fibrosis** syndrome. The aim of the present study is to determine the effects of several intraperitoneal antibiotics on human peritoneal mesothelial cell (HPMC) growth at their usual loading and maintenance doses. HPMCs were isolated from human omenta. Proliferation of HPMC was evaluated by modified methyltetrazolium assay and cell membrane integrity was assessed by lactate dehydrogenase method. The results showed that most cephalosporins exert an inhibitory, even toxic, effect on HPMCs at their loading doses. Cephalothin, cephradine, cefamandole, cefoxitin, cefuroxime and cefoperazone inhibited HPMC proliferation at their maintenance doses. Vancomycin, clindamycin, aztreonam, piperacillin, imipenem, tobramycin and ceftriaxone have no effect in their usual intraperitoneal doses. From the viewpoint of peritoneal protection, not only drug sensitivity of the causative microorganisms but also effects of antibiotics on HPMC regeneration should be considered when selecting antibiotics for CAPD peritonitis.

D2: Liver. 1994 Oct;14(5):225-9.

Flucloxacillin-associated hepatic injury.

Koek GH, Stricker BH, Blok AP, Schalm SW, Desmet VJ.

Department of Internal Medicine, University Hospital Gasthuisberg, Leuven, Belgium.

ABSTRACT: Eleven cases of hepatic injury attributed to the intake of flucloxacillin were reported to the Netherlands Center for Monitoring of Adverse Reactions to Drugs between 1982 and 1992. They concerned four men and seven women, with a mean age of 57 years, treated for 2-28 days with an oral dose varying from 1500-4000 mg per day. Symptoms mostly appeared 10 to 30 days after starting treatment with flucloxacillin. Biochemically, the pattern was compatible with cholestatic hepatitis in seven cases, with a mixed cholestatic-hepatocellular type of injury in one case, a hepatocellular pattern in two cases, and mild liver enzyme elevations in one patient. Two patients died, one due to fatal bleeding from the liver after biopsy, and the second patient to a combination of hepatic and cardiac failure. The other

patients recovered, on average 72 days after peaking of serum aminotransferase values. Histology in seven cases showed cholestatic hepatitis in five, with cholangitis or cholangiolitis in four of these patients. In the other two patients, there was centrilobular cholestasis with extensive **bridging fibrosis** and portal-central bridging necrosis, respectively.

D3: Pathology. 1993 Jul;25(3):223-8.
Flucloxacillin induced liver disease: histopathological findings at biopsy and autopsy.
Eckstein RP, Dowsett JF, Lunzer MR.
Department of Anatomical Pathology, Royal North Shore Hospital, St. Leonards, Sydney NSW.

ABSTRACT: The histological appearances of liver biopsies of 13 patients who developed cholestasis following courses of flucloxacillin are presented. In most of the cases jaundice and pruritus were protracted and in nearly all cases liver function tests are yet to return to normal after mean follow-up of 18 mths. One patient died after 7 mths of jaundice and another shows clinical evidence of secondary biliary cirrhosis. Biopsies typically showed hepatocellular and canalicular bile stasis with minimal or no hepatitis. Mild **portal fibrosis** and a patchy portal lymphocytic infiltrate were usually present. In 4 cases bile ducts were reduced in number and in 6 cases reduced in size. Bile duct epithelium showed degenerative changes but only occasional infiltration by inflammatory cells. Ductular proliferation was quite variable and in some cases--most noticeably the fatal case--was inconspicuous despite depletion of bile ducts. The appearances suggested damage not only of hepatocytes but also of bile ducts and proliferating ductules. This may explain the prolonged and occasionally irreversible hepatic disease associated with the use of flucloxacillin. Flucloxacillin should be included amongst the causes of vanishing bile duct syndrome.

INDUCING AGENT: DRUGS (D4-D8)

D4: Rev Mal Respir. 1992;9(6):593-601.
[Drug-induced pulmonary diseases: diagnostic, therapeutic and prognostic aspects. Apropos of 10 personal case reports]
[Article in French]
Chabot F, Aymard B, Lesur O, Kheir A, Moreau L, Cornette A, Gerard H, Delorme N, Polu JM.
Service des Maladies Respiratoires et Reanimation Respiratoire, Brabois, Vandoeuvre-les-Nancy.

ABSTRACT: The authors report ten cases of drug induced lung diseases, complicated by respiratory failure of whom five were attributed to cytotoxic drugs and five to non cytotoxic drugs. The drug induced lung disease presented as acute respiratory distress syndrome in two cases, alveolar interstitial lung disease in three cases, purely interstitial in five cases. There was acute respiratory failure (ARF) in eight cases and chronic respiratory failure (CRF) in two cases. Among the five patients admitted for cytotoxic

drug induced lung disease and ARF, four recovered and one died of diffuse destructive pulmonary fibrosis. Among the five patients having non cytotoxic drug induced lung disease, three were in ARF and recovered. The other two had CRF and died of diffuse **pulmonary fibr sis**. The diagnostic of drug induced lung disease was established in each case with the chronology of the clinical events, the exclusion of other possible causes of the lung disease and the evolution after removal of the incriminated drug. Broncho-alveolar lavage (BAL) had a major diagnostic value. It was contraindicated by respiratory failure in five cases. The predominant alveolar cell type was lymphocyte (four cases), eosinophil (three cases) and neutrophil (one case), BAL was realized with a provocation test and demonstrated the pathogenic role of cyclothiazide in one case. No specific information was given by histology. The prognosis did not seem to be linked to the severity of the initial clinical picture, or to the nature of the underlying neoplastic disorder, but to the degree and evolution of the **pulmonary fibrosis**.

D5: Jpn J Med. 1990 May-Jun;29(3):248-54.
Clinical evaluation of 12 cases of antimicrobial drug-induced pneumonitis.
Kohno S, Yamaguchi K, Yasuoka A, Koga H, Hayashi T, Komori K, Hara K.
Second Department of Internal Medicine, Nagasaki University School of Medicine, Japan.

ABSTRACT: The diagnosis of drug-induced pneumonitis is generally difficult, and it is made clinically by Tamura's criteria. We experienced 12 cases (7 definite and 5 possible cases) of antimicrobial drug-induced pneumonitis (one of case was the first case caused by carbapenem). Symptoms such as fever (11/12), cough (10/12) and dyspnea (10/12) and laboratory data such as eosinophilia (7/12), elevation of IgE (4/6) and hypoxia (11/12) were commonly seen in these patients, although they were not specific. Lymphocyte stimulation test (5/11) and provocation test (4/8) were quite suggestive of drug allergy. Bronchoscopy has been used for confirmation of pneumonitis. Transbronchial lung biopsy revealed alveolitis (4/9) or **alveolar fibrosis** (3/9), and bronchoalveolar lavage showed lymphocytosis (6/6) and depression of OKT4/T8 ratio (3/5). The combination of bronchoscopic and immunological examinations were more confirmative for diagnosis.

D6: J Mol Cell Cardiol. 1996 Jun;28(6):1279-85.
Wound healing following myocardial infarction in the rat: role for bradykinin and prostaglandins.
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Department of Internal Medicine, University of Missouri Health Sciences Center, Columbia 65212, USA.

ABSTRACT: Bradykinin and prostaglandins are established mediators of exudative and inflammatory phases of healing. Their contribution to the fibrogenic component of healing in the heart is less certain. We therefore undertook the present study in rats with acute myocardial infarction (MI) following left coronary artery ligation. Treatment with a bradykinin B2 receptor antagonist (Hoe140, 0.5 microgram/kg/min s.c.) or a cyclooxygenase inhibitor (indomethacin, 2 mg/kg p.o.), initiated 24 h after

surgery, was examined for responses in MI topography (size and area), MI and nonMI tissue **fibrosis** (fibrillar collagen specific picrosirius red). Early (week 1) and late (week 4) phases of fibrogenesis postMI were examined. Compared to control, we found: (1) MI size at weeks 1 and 4 was comparable in untreated and treated rats: (2) infarct area, a measure of scar thickness, was reduced ($P < 0.05$) at week 4 by each intervention; and (3) densitometric collagen volume fraction did not reveal a reduction in collagen accumulation at the MI site, but this was evident remote to the MI ($P < 0.05$) at week 4 for each agent. Thus, pharmacological interference with bradykinin-receptor binding or prostaglandin synthesis following MI is associated with reduced fibrillar collagen formation. Though the mechanism responsible for observed alteration in fibrogenesis is uncertain, anti-inflammatory and anti-proliferative properties of these agents may be responsible.

D7: Cardiovasc Res. 1996 Apr;31(4):546-54.

Angiotensin II-induced myocardial fibrosis in rats: role of nitric oxide, prostaglandins and bradykinin.

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ABSTRACT: OBJECTIVE: Chronic elevations in plasma angiotensin II (AngII) are associated with an efflux of plasma macromolecules into the perivascular and contiguous interstitial space. This is followed by the appearance of macrophages and type I collagen-producing, fibroblast-like cells that precede the accumulation of fibrous tissue at these sites. Whether this **perivascular and interstitial fibrosis** is a direct effect of AngII on collagen turnover of these cells or an indirect response mediated by nitric oxide, prostaglandins and/or bradykinin released in response to AngII, is uncertain. METHODS: We measured **perivascular and interstitial fibrosis** (picrosirius-stained tissue) in response to 14-day infusion of AngII (150 ng/kg/min, s.c.) in male Sprague-Dawley rats. Treated animals were compared to untreated controls and to groups receiving AngII together with either an NO-synthase inhibitor [NG-nitro-L-arginine methyl ester (L-NAME) 10 mg/kg/day in drinking water], a cyclo-oxygenase inhibitor (indomethacin, 2 mg/kg/day in drinking water), or a bradykinin B2 receptor antagonist (Hoe140, 115 ng/kg/min, s.c.). RESULTS: When left and right ventricles of treated rats were compared to untreated controls, AngII led to a respective 68 and 48% increase in perivascular collagen volume fraction (PCVF) and a 54 and 22% increase in interstitial collagen volume fraction (ICVF). Co-administration of AngII + L-NAME did not attenuate either PCVF or ICVF while indomethacin significantly attenuated PCVF by 37 and 33% of left and right ventricle, respectively, but did not alter ICVF in either ventricle when compared to AngII-treated animals. Co-administration of AngII + Hoe140 completely prevented perivascular and interstitial collagen accumulation with the extent of perivascular fibrosis comparable to untreated controls. CONCLUSION: The perivascular and interstitial fibrosis of the rat right and left ventricles seen in association with the exogenous administration of AngII is mediated by the release of bradykinin and prostaglandins, and therefore is an indirect response to elevated circulating AngII.

D8: Rev Pneumol Clin. 1996;52(1):33-5.
[Fibrosing pneumopathy caused by labetalol]
[Article in French]
Kheir A, Chabot F, Delorme N, Polu JM.
Service de Medecine A, CH Remiremont.

ABSTRACT: A diffuse **interstitial pulmonary fibrosis** occurred in a 74-year-old woman treated for ten years with labetalol for systemic hypertension. Bronchoalveolar lavage (BAL) revealed lymphocytic and neutrophilic alveolitis. The lack of another etiologic factor and the spontaneously favorable course after withdrawal of the drug support the hypothesis of a labetalol induced pulmonary fibrosis.

INDUCING AGENT: BACTERIAL INFECTION (D9)

D9: J Reprod Med. 1991 Jul;36(7):543-5.
Advanced actinomycotic pelvic inflammatory disease simulating gynecologic malignancy. A report of two cases.
Hoffman MS, Roberts WS, Solomon P, Gunasekarin S, Cavanagh D.
Department of Obstetrics and Gynecology, University of South Florida College of Medicine, Tampa.

ABSTRACT: Two women had large, solid, fixed pelvic masses simulating advanced ovarian cancer in one case and advanced cervical cancer in the other. Both patients had had plastic intrauterine contraceptive devices in situ for 7 and 17 years, respectively. Both patients required laparotomy to make the diagnosis. In both the surgery was markedly difficult because of the total absence of tissue planes. Both had obvious actinomycotic disease on routine histologic examination of the ovary and were treated with prolonged penicillin, with some, but not total, resolution of the **pelvic fibrosis**. The diagnosis of advanced actinomycotic pelvic inflammatory disease should be entertained in patients with a large, solid pelvic mass and an intrauterine device in situ or a recent history of intrauterine device use.

INDUCING AGENT: CHEMOTHERAPY (D10)

D10: Int J Radiat Oncol Biol Phys. 1997 Jul 15;38(5):1013-8.
Accelerated fractionation in esophageal cancers: a multivariate analysis on 88 patients.
Girinsky T, Auperin A, Marsiglia H, Dhermain F, Randrianarivelo H, Kac J, Ducreux M, Elias D, Rougier P.
Department of Radiation Oncology, Institut Gustave Roussy, Villejuif, France.

ABSTRACT: PURPOSE: Accelerated fractionation was used to shorten overall treatment time to increase locoregional control and cause-specific survival. METHODS AND MATERIALS: Eighty-eight patients with cancer of the esophagus ineligible for surgery were entered in the study between 1986 and 1993. Neoadjuvant chemotherapy was given to 64% of patients. Accelerated radiotherapy using the concomitant boost technique delivered a median dose of 65 Gy in a median overall treatment time of 32 days. RESULTS: The 3-year actuarial local control rate in patients with T1, T2, and T3 tumors was 71%, 42%, and 33%, respectively. The 3-year cause-specific survival rates were 40%, 22%, and 6%, respectively. Sixteen percent of patients experienced Grade 3 esophagitis. Late toxicity included esophageal stenosis and **pulmonary fibrosis** in 8% and 9% of the patients, respectively. Multivariate analysis demonstrated that T stage and overall treatment time were prognostic factors for cause-specific survival. T stage and neoadjuvant chemotherapy were independent prognostic factors for locoregional control. CONCLUSION: These findings suggest that accelerated fractionation given in an overall treatment time of <35 days might be beneficial for early-stage cancer of the esophagus. Neoadjuvant chemotherapy is not recommended, as it was a significant adverse prognostic factor in the multivariate analysis for local control. Accelerated fractionation can be carried out with moderate acute and late toxicity.

INDUCING AGENT: DISEASE (D11-D12)

D11: J Am Soc Nephrol. 1997 Apr;8(4):684-8.

Obstructive nephropathy as a result of retroperitoneal fibrosis: a review of its pathogenesis and associations.

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Department of Medicine, Milton S. Hershey Medical Center, Pennsylvania State University College of Medicine, Hershey 17033, USA.

ABSTRACT: **Retroperitoneal fibrosis** is a rare disease, typically with an insidious clinical course. It is thought that this disease process is perhaps an exaggerated reaction to an inciting inflammatory event. In this study, a case of retroperitoneal fibrosis is reported, in which the patient presented with typical symptoms of retroperitoneal fibrosis, along with some atypical vasculitic symptomatology. Retroperitoneal fibrosis is a disease process with an unknown etiology, which has been observed to be associated with a number of different possible inciting factors. Two factors that have been documented in the literature as being associated with retroperitoneal fibrosis include the use of beta-blocking agents, and connective tissue disease processes such as systemic lupus erythematosus. The patient discussed was using beta-blocker medication and also had signs and symptoms suggestive of a lupus syndrome. There are no reported cases of the combined association of beta-blocker usage, lupus, and retroperitoneal fibrosis.

D12: Dtsch Med Wochenschr. 1997 Mar 14;122(11):323-7.

[Immunogenic hyperthyroidism with hyperdynamic heart failure and early cirrhotic transformation of the liver]

[Article in German]

Fischer MR, Spes CH, Huss R, Gartner R.

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ABSTRACT: HISTORY AND CLINICAL FINDINGS: A 58-year-old woman was admitted because of jaundice, ascites and marked oedema. For three years she had suffered from nervousness, decreasing fitness and weight loss, which had been assumed as due to chronic alcoholism. Liver biopsy revealed extensive **fibrosis**, in part with early cirrhotic transformation. This was followed by cardiac failure with atrial fibrillation (ventricular rate 140/min) and marked pleural effusions. The thyroid was diffusely enlarged and there were signs of exophthalmos. INVESTIGATIONS: Bilirubin concentration was 3 mg/dl, lactate dehydrogenase activity was 310 U/l, cholesterase 1.3 kU/l and the prothrombin test was 21%. The TSH level was 0.01 microU/ml while the free thyroxine level was 4.7 ng/dl and that of free triiodothyronine 13.5 pg/ml. Chest radiograph revealed cardiomegaly, bilateral peripheral pulmonary congestion and pleural effusions to midfield. Right heart catheterization excluded pulmonary hypertension; cardiac output was 10l/min. The thyroid was enlarged on ultrasound and diffusely echopoor, as in immune thyroid disease. TREATMENT AND COURSE: Cardiac failure regressed and thyroid function normalized within ten days on propranolol, 4 x 40 mg and thiamazole 3 x 40 mg daily intravenously. Subtotal thyroidectomy was performed three weeks later with subsequent thyroid hormone substitution. Liver functions were normal six months later and ultrasound showed no signs of cirrhotic change and the ascites had resolved. CONCLUSION: Hyperthyroidism is frequently associated with changes in liver functions. In extreme cases, high-output cardiac failure may occur, with liver congestion and clinical as well as histological changes like those in liver cirrhosis.

INDUCING AGENT: AUTOIMMUNITY (D13)

D13: Cardiovasc Drugs Ther. 1995 Oct;9(5):701-7.

Experimental rat model representing both acute and chronic heart failure related to autoimmune myocarditis.

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ABSTRACT: The most important clinical manifestation of myocarditis is congestive heart failure. The precise mechanisms of heart failure during myocarditis have not been elucidated because no animal model that would permit in vivo study of hemodynamics in severe active myocarditis has been available. We monitored hemodynamics and left ventricular function in a rat model of experimental autoimmune myocarditis to determine if this model could be useful for the study of in vivo hemodynamics in severe active myocarditis. Lewis rats were immunized with human cardiac myosin suspended in complete

Freund's adjuvant. Baseline hemodynamics were measured using an ultraminiature catheter pressure transducer via the right internal carotid artery, 4 weeks after immunization in one group of rats (acute phase) and 3 months after immunization in another group (chronic phase). Untreated rats served as the control group. Hemodynamic measurements were also obtained after infusion of dobutamine in the acute-phase and chronic-phase groups. The heart weight-to-body weight ratios were significantly higher in both the acute-phase group and the chronic-phase group compared with normal control rats. The baseline left ventricular systolic pressure was significantly lower in the chronic phase group than in the control group. Peak dP/dt and peak -dP/dt were significantly lower in both the acute-phase group and the chronic-phase group compared with the control group. Dobutamine significantly increased left ventricular systolic pressure, peak dP/dt, and peak -dP/dt in the chronic-phase group but caused only minor changes in hemodynamic variables in the acute-phase group. In vivo measurements of hemodynamic variables indicated the presence of left ventricular dysfunction in rats with experimental autoimmune myocarditis. This animal model may be useful for the study of both acute heart failure related to acute myocarditis and chronic heart failure due to **diffuse myocardial fibrosis**.

INDUCING AGENT: RADIATION (D14-D16)

D14: Int J Radiat Biol. 1997 Aug;72(2):227-34.
Annexin I in fibrotic rat lung and cultured lung fibroblasts following irradiation.
Ts'ao C, Ward WF, Tsao FH, Taylor JM, Molteni A.
Department of Pathology, Northwestern University Medical School, Chicago, IL 60611, USA.

ABSTRACT: **Radiation-induced lung fibrosis** is a result of collagen accumulation in the interstitium, partly due to increased collagen synthesis by fibroblasts. One feature of active collagen synthesis is increased membrane trafficking in the fibroblasts. A group of proteins called annexins is believed to play a regulatory role in membrane fusion and exocytosis. Therefore, increased annexin activity might be expected in the fibrotic lung. We tested this hypothesis by measuring annexin I levels, hydroxyproline content and ultrastructural changes in radiation-induced pulmonary fibrosis in rat. Three months after a single exposure to 30 Gy of X-rays to the right hemithorax, the right lung of the rat was atrophied and fibrotic with a concomitant increase in size of the shielded left lung. Electron micrographs revealed that the irradiated lung was ladened with interstitial collagen fibrils, with increased number of fibroblasts amongst them. Hydroxyproline concentration in the irradiated lung was nearly twice that in the sham-irradiated lung. Annexin I in the irradiated lung, on the other hand, was markedly reduced, and barely detectable on immunoblots. Since increased annexin I might precede enhanced collagen production, we also measured annexin I levels in rat lungs 3 days after 30 Gy irradiation and correlated that with hydroxyproline concentration. We found no appreciable difference in annexin I levels and hydroxyproline content between sham-irradiated and irradiated lungs at 3 days. To determine whether annexin I levels in cultured fibroblasts were altered by irradiation, we assayed annexin I in cultured rat lung fibroblasts 3

days after 0.10 Gy exposure, with concomitant measurement of 14C-proline incorporation. The annexin I level in fibroblasts irradiated with 10 Gy X-rays was 55% higher than in sham-irradiated fibroblasts. However, incorporation of 14C-proline into collagenase-sensitive macromolecules in the culture medium and extracellular matrix was not different between these two groups of cells. These data demonstrate a radiation-induced increase in immunoreactive annexin I in cultured lung fibroblasts, but fail to support the hypothesis of a positive correlation between annexin I concentration and fibrosis in irradiated rat lung.

D15: Int J Radiat Oncol Biol Phys. 1997 Aug 1;39(1):187-95.

Increased transforming growth factor beta (TGF-beta) immunoreactivity is independently associated with chronic injury in both consequential and primary radiation enteropathy.

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Department of Surgery, University of Arkansas for Medical Sciences, Little Rock 72205, USA.

ABSTRACT: PURPOSE: Radiation enteropathy is characterized by sustained increase in transforming growth factor beta (TGF-beta) immunoreactivity and connective tissue mast cell (CTMC) hyperplasia that may be responsible for progressive **fibrosis** and lead to clinical complications. We examined to what extent these chronic molecular and cellular phenomena are associated with acute mucosal breakdown (consequential injury) and/or direct (primary) radiation injury in late-responding compartments. METHODS AND MATERIALS: Rat small intestine was exposed to 50.4 Gy x-irradiation given either over 18 days (2.8 Gy daily or 5.6 Gy every other day) or 9 days (2.8 Gy twice daily or 5.6 Gy daily). Intestinal complications were recorded and groups of animals were euthanized at 2 and 26 weeks to assess subacute and chronic injury. Histopathologic changes were assessed with a radiation injury scoring system (RIS), total TGF-beta immunoreactivity was quantified with computerized image analysis, and CTMC hyperplasia was assessed in toluidine blue-stained sections. RESULTS: TGF-beta immunoreactivity and CTMC hyperplasia colocalized in areas of injury and were highly significantly correlated. Increased fraction size and decreased overall treatment time were associated with increased RIS ($p < 0.01$ and $p < 0.00001$), increased TGF-beta immunoreactivity ($p = 0.01$ andp < 0.001), and degree of CTMC hyperplasia ($p = 0.01$ and $p < 0.001$). Postradiation CTMC numbers increased across treatment groups from 2 to 26 weeks ($p < 0.01$). TGF-beta immunoreactivity was independently associated with chronic intestinal wall fibrosis ($p = 0.003$). CONCLUSION: This in vivo study supports in vitro evidence linking increased TGF-beta immunoreactivity and mast cell hyperplasia and strongly suggests their involvement in the molecular pathogenesis of both primary and consequential radiation enteropathy.

D16: Hepatology. 1997 Jul;26(1):128-34.

Severe radiation-induced liver disease following localized radiation therapy for biliopancreatic carcinoma: activation of hepatic stellate cells as an early event.

Sempoux C, Horsmans Y, Geubel A, Fraikin J, Van Beers BE, Gigot JF, Lerut J, Rahier J.

Department of Pathology, University Hospital St-Luc, Louvain Medical School, Brussels, Belgium.

ABSTRACT: Radiation-induced liver disease is recorded as a form of veno-occlusive disease. Its pathogenesis remains unclear even if the initial injury likely occurs in the endothelial cells of central veins. The aim of our study was to investigate liver morphological features in relation to alpha-isoform of smooth muscle actin expression in hepatic stellate cells in six patients treated by localized radiotherapy on the biliopancreatic area. Within the month after completion of treatment, an activation of hepatic stellate cells strictly confined to irradiated areas and coinciding with congestive changes was observed. At a later stage, collagen deposition gradually increased, replacing the congestive and destroyed areas. This new fibrotic tissue also contained numerous alpha-smooth muscle positive cells. Our data suggest that early hepatic stellate cells activation coinciding with congestive changes plays an important role in radiation liver injury and ensuing **fibrosis**.

INDUCING AGENT: SURGERY (D17-D20)

D17: J Cardiovasc Pharmacol Ther. 1997 Oct;2(4):331-335.
A Therapeutic Commentary.
DeQuattro V V, Li D.
Division of Cardiology, University of Southern California School of medicine, Los Angeles, California, USA

ABSTRACT: Thirty-one million patients in the United States undergo surgical procedures every year. Approximately 10%-the majority of these with hypertension-are at an increased risk for perioperative and postoperative cardiovascular morbidity and mortality. Thus, hypertensive patients requiring surgery, especially the 2.1 million undergoing noncardiac procedures, should be evaluated carefully for the magnitude, and if severe, the cause of the hypertension. Additionally, their associated metabolic and cardiovascular status should be characterized and corrected with aggressive therapy. Hypertensive patients with known ischemic heart disease, those with multiple risk factors for ischemic heart disease (IHD), some with valvular heart disease, and those with congestive heart failure should be evaluated for their ability to perform the physical and social activities of everyday life, and, when necessary, have formal stress testing. Most studies suggest that blood pressures of 180/110 mm Hg or greater are associated with a greater risk for perioperative ischemic events. Therefore, the goals of blood pressure control should be to reduce the blood pressure without jeopardizing organ function. Antihypertensive medication should be administered until the time of surgery. beta-Receptor blockers should be instituted or continued in patients with angina and in some patients with congestive heart failure. Those without prior antihypertensive therapy might be best treated with beta-blocker therapy perioperatively as evidenced by the Multicenter Study of Perioperative Research Group with atenolol and those earlier studies with metoprolol. The risks of the surgery should be discussed with the patient so the risks can be weighed against the expected benefit. Studies suggest that perioperative risk for any patient, and especially patients with hypertension, are in part related to the adrenergic arousal before, during, and

after the procedure as evidenced by the rise in heart rate and blood pressure, along with the liberation of clotting facators and increased risk for plaque rupture, coronary vasoplasm, and consequent myocardial infarction and **fibrosis**.

D18: Laryngoscope. 1997 Aug;107(8):1107-11.
Argon laser irradiation to the semicircular canal.
Sugio Y, Nomura Y, Oki S.
Department of Otolaryngology, Showa University, Tokyo, Shinagawa-ku, Japan.

ABSTRACT: In order to elucidate the effects of argon laser irradiation on the lateral semicircular canal of the guinea pig, the vestibular labyrinth was histologically studied after irradiation, using the conventional celloidin method. Irrigation of the external meatus with ice water was used to evaluate the function of the semicircular canal by recording caloric nystagmus. When irradiation was performed, a laser probe was approximated to the lateral canal, 0.5 to 1 mm away from the surface of the canal. Each time, power applied was 1.0 W on the dial of the laser machine. The duration of irradiation was 0.5 s. The lateral canal was irradiated one to 15 times. Twenty-five to 87 days after irradiation, the temporal bones were fixed in Heidenhein-Susa solution, removed, and subjected to celloidin processing. The irradiated bony wall of the lateral canal demonstrated charring. Lucent areas were observed around and under the charred area. The semicircular duct showed shrinkage with disappearance of the trabecular mesh. New bone formation was observed along the endosteum of the irradiated area. The lateral canal was completely occluded by ossification with or without **fibrosis** when sufficient energy was applied. The anterior and posterior canals were normal. Caloric tests using 5 mL of ice water for 5 s failed to elicit nystagmus on the irradiated side.

D19: Klin Monatsbl Augenheilkd. 1997 Aug;211(2):106-12.
[Long-term outcome after implantation of various intraocular lenses through a corneal tunnel]
[Article in German]
Dick B, Kohnen T, Jacobi F, Jacobi KW.
Universitats-Augenklinik Mainz.

ABSTRACT: A prospective, randomized study was carried out to evaluate functional and biomicroscopic long-term results of different posterior chamber intraocular lenses (IOLs) over a period of two years after clear corneal cataract surgery. PATIENTS AND METHODS: 2 years after phacoemulsification through a temporal two-step clear corneal incision a total of 67 patients were examined. In 26 eyes (group A) a foldable plate-haptic silicone IOL (Chiron Adatomed, C10), in 25 eyes (group B) a foldable disc silicone IOL (Chiron Adatomed, 90D) had been implanted through a 3.5 (group A) or 4 mm (group B) corneal incision using a cartridge injector. In 16 eyes (group C) a one-piece PMMA-IOL (Pharmacia & Upjohn, 809C) had been implanted through a 5 mm incision. All eyes underwent functional and biomicroscopic examinations, as well as computerized videokeratographic analysis to

obtain corneal topography data. RESULTS: In group A uncorrected visual acuity valued 0.64 (+/-0.29 SD), in group B 0.59 (+/-0.24) and in group C 0.56 (+/-0.27). Median of uncorrected visual acuity was 0.6 for all groups. Corrected visual acuity was 0.81 (+/-0.29) in group A, 0.8 (+/-0.25) in group B and 0.83 (+/-0.3) in group C. Intraocular pressure (mm Hg) was 13 (+/-2.5) in group A, 14.7 (+/-2) in group B and 15.1 (+/-2.5) in group C. **Fibrosis** of the anterior capsular rim occurred in 42% of the cases. One eye demonstrated folds in the posterior capsule (group B). Posterior capsular opacification valued 11.9% for all groups. In one eye a Nd:YAG-capsulotomy had already been performed. In group A a decentration of more than 1 mm was objected in one case, in group B in two cases and in group C in one case, but no patient complained about any functional impairment. Two years postoperatively, no signs of a re-flattening in the incision area could be detected using difference mapping tools in the videokeratographic analysis. CONCLUSION: Two years after implantation of foldable silicone IOLs and PMMA-IOLs via a temporal clear corneal tunnel incision after phacoemulsification only slight functional and morphologic differences between the three IOL-types could be observed.

D20: Am J Otol. 1997 Jul;18(4):408-12.
Functional hearing results in revision stapes surgery.
Magliulo G, Cristofari P, Terranova G.
IV ENT Clinic, University La Sapienza, Rome, Italy.

ABSTRACT: OBJECTIVE: The object of our study was to review the results of 63 revision stapes surgeries performed from 1978 to 1994. RESULTS: The most common cause of failure was the displacement of the prosthesis, followed by ossicular chain problems and **oval window fibrosis**. Postoperative hearing improvement within a 20-dB air-bone gap was achieved in 58.7% of the patients. Hearing gain was closely linked to the operative findings. Better results occurred when prosthesis problems were found. Evaluation of the hearing results by using Glasgow benefit plot gave evidence of symmetric normal hearing in only 40% of the cases. CONCLUSIONS: Prevention of the cause of failure during the primary stapes surgeries, lessening the surgical trauma, seems to provide the most favorable hearing results.

INDUCING AGENT: SURGERY GRAFT (D21)

D21: J Biomed Mater Res. 1997 Aug;36(2):200-8.
Development and characterization of an alginate-impregnated polyester vascular graft.
Lee JH, Kim WG, Kim SS, Lee JH, Lee HB.
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ABSTRACT: Alignate gels are known to be biocompatible, degradable, and nontoxic. In this study, sodium alginate was impregnated into a porous, knitted polyester graft (Microvel double velour graft) 6 mm in diameter. The alginate-impregnated graft was investigated in vitro and in vivo to evaluate its

potential for use as a new vascular graft impervious to blood, while retaining high porosity for tissue ingrowth and biological healing. For in vitro investigation, the coating weight, water permeability, morphology, and mechanical properties of the alginate-impregnated grafts were compared to those of control or commercially available collagen-impregnated (Hemashield) grafts. The water permeability of the controls (1846 mL/min.cm2 at 120 mm Hg) was reduced > 99% by the alginate impregnation, rendering the graft impervious to blood. The coating weight of the alginate was 45 mg/g of graft, producing a much lower value than that of the collagen-impregnated model (310 mg/g). For in vivo investigation, the alginate-impregnated grafts were implanted in the aorta of mongrel dogs without preclotting for scheduled periods ranging from 4 h to 6 months. The control grafts after preclotting and the collagen-impregnated grafts without preclotting were also implanted for 3 and 6 months for comparison. Gross observation of the explanted grafts and histologic examination of the representative sections were conducted for three types of grafts using a light microscope after hematoxylin-eosin staining. No significant differences were observed between the histologic appearance of the alginate-impregnated grafts and that of the preclotted and collagen-impregnated grafts in terms of the degree of inflammation, foreign-body giant cell reaction, and **intimal fibrosis**. Endothelial-like cells were present on the midsections of all the grafts after 3 months of implantation. The resorption rate of alginate impregnated into the graft was also examined after staining the sections with periodic acid-Schiff reagent, Toluidine blue, and Alcian blue, which are specific for alginates. The staining alginate was partially visible between the graft fabrics up to 1 month after implantation, but was completely resorbed after 3 months. This preliminary study demonstrated that the use of an alginate as a biological sealant instead of proteins such as collagen, gelatin, and albumin may be a feasible approach to developing imprevious textile arterial prostheses, since the proteins have been reported to be generally unstable, hard to obtain in pure forms, not easy to crosslink and control resorption rate, and difficult to render compatible with standard storage and sterilization procedures.

INDUCING AGENT: CADMIUM (D22)

D22: J Toxicol Sci. 1997 Aug;22(3):185-98.

Long-term, low-dose, cadmium-induced nephropathy with renal osteopathy in ovariectomized rats.

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ABSTRACT: To establish an animal model of chronic cadmium nephropathy and osteopathy, we intraperitoneally administered 0.228 mg CdCl2 (Cd) or normal saline (NS) to 52 female Sprague-Dawley (S.D.) rats 3 times a week for 16 months following ovariectomy (OV) or sham surgery (Sham), dividing the animals into three experimental groups (OV-Cd, Sham-Cd and OV-NS). Two groups of male S.D. rats were also administered Cd or NS (22 animals; Male-Cd and Male-NS). Cd-administered rats gained

significantly less body weight than NS rats after 16 months of experiments with no signs of emaciation. Serum creatinine levels and Cd contents in the kidney had significantly increased in the Cd-administered rats. OV-Cd rats showed significant decreases in PTH levels and increases in calcium contents in the kidney and other organs. Kidneys of Cd-administered rats showed atrophy, dilatation, and **interstitial fibrosis** of tubules. Sclerosis and collapse of the glomeruli were observed in the Cd groups with no proliferation in mesangial cells or matrix. The Haversian canal system of the Cd-administered rats disappeared and was replaced by a large quantity of degenerated, necrotic, and restorative tissues. Bone histomorphometric parameters showed that osteoid volume and osteoid surface had significantly increased in the Male-Cd group. In contrast, decreases in bone mass and increases in fibrous tissue were found to be more prominent in the OV-Cd group. Our results have demonstrated for the first time that long-term, low-dose CdCl2 administration to ovariectomized S.D. rats is capable of inducing irreversible nephropathy with osteopathy exhibiting pathological and bone histomorphometric characteristics that are very similar to those of Itai-Itai disease.

INDUCING AGENT: WAR WOUNDS (D23)

D23: J Urol. 1997 Aug;158(2):421-4.

Experience with 30 posttraumatic rectourethral fistulas: presentation of posterior transsphincteric anterior rectal wall advancement.

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ABSTRACT: PURPOSE: We present the challenging problems involving the treatment of rectourethral fistulas, especially those caused by war wounds. Various existing techniques used by a single surgeon are compared in this study. The method of posterior transsphincteric anterior rectal wall advancement is described as the treatment of choice. We emphasize the importance of fecal and urinary diversion. To our knowledge this series is the largest in the literature. MATERIALS AND METHODS: From 1981 to 1994 we treated 30 men 18 to 50 years old (mean age 34) with posttraumatic rectourethral fistulas, including 23 (76.5%) caused by missiles. Urethroscopy with digital examination under anesthesia was the most reliable diagnostic study. End sigmoid colostomy and suprapubic cystostomy were performed in all patients. RESULTS: In 14 patients (46.5%) the fistula healed after double diversion but 16 (53.5%) required reconstruction for repair. Of the 6 procedures using established techniques in 5 patients 3 (50%) failed and 3 were successful but a urethral stricture developed after 2 (66%). On the other hand, in all patients (100%) who underwent repair via posterior transsphincteric anterior rectal wall advancement the fistula resolved and a stricture developed in 3 (27%). Fistula size and extent of **fibrosis** affected treatment, while etiology did not. Urethral obstruction complicated only the missile wounds. CONCLUSIONS: Double diversion has resulted in resolution of approximately half of the small, less fibrous fistulas. Early repair is recommended for large fibrous fistulas. Anterior rectal wall advancement

through a posterior transsphincteric incision offers a new option that has proved to be successful and safe, and causes fewer urethral complications. It also provided good visualization with minimal bleeding and was less painful. Double diversion is a prerequisite to reconstruction.